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Injection Site Granulomas Resulting from Administration of Leuprorelin Acetate

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1. Introduction

Leuprorelin acetate is a luteinizing hormone releasing hormone (LHRH) agonist and was launched in 1997. It has been used for sex hormone-dependent diseases such as prostate cancer, endometriosis, premenopausal breast cancer, and central precocious puberty. In Japan, a preparation for administration at monthly intervals (Leuprin®) has been available since 1999, and a continuous sustained release preparation for administration every 3 months (Leuprin SR®) since 2002. In recent years, there has been a considerable increase in the frequency of foreign body granulomas, particularly in patients in whom a 1-monthly preparation was changed to a 3-monthly continuous sustained release preparation. We report two such cases that we encountered and present a literature review.

2. Case

Case 1: A 77-year-old Japanese male had been treated for prostate cancer with monthly subcutaneous injections of depot leuprorelin acetate since August 2005. In December 2005, his treatment was changed to the 3-monthly leuprorelin acetate preparation. One month later, he presented with a nodule at the injection site. The nodule was 15 mm in diameter, firm and tethered to the overlying skin (**Photograph 1**). Skin biopsy revealed a granuloma with epithelioid cells, and multinucleated giant cells were observed in the subcutaneous tissue by hematoxylin-eosin staining. The granuloma contained vacuoles of various sizes, and portions of it were phagocytosed (**Photograph 3**). In addition, inflammatory cell infiltration was observed, mainly of lymphocytes and neutrophils, along with eosinophils (**Photograph 4**).

His treatment was then changed to goserelin acetate (Zoladex®) for subsequent injections, no problems occurred thereafter.

Case 2: A 78-year-old Japanese male had been treated for prostate cancer with monthly subcutaneous injections of depot leuprorelin acetate since October 2002. In February 2003, his treatment was changed to the 3-monthly preparation. After the sixth administration, he presented with a nodule at the injection site.

Laboratory tests showed no abnormalities in blood count, blood biochemistry, and urine. Serum PSA was high at 5.14 ng/ mL, while γ -SM was within normal limits (0.4 ng/ mL).

The nodule was 30 × 35 mm in diameter, painless, firm, and tethered to the overlying skin (**Photograph 2**).

Skin biopsy showed a granuloma with epithelioid cells and multinucleated giant cells, and lymphocytes were observed from the subdermal layer to the subcutaneous tissue (**Photograph 5**). His treatment was changed to goserelin acetate (Zoladex®) for subsequent injections, and no problems occurred thereafter.

Intradermal and patch tests were not performed in either patient because we were unable to obtain consent from them.



Fig. 1. Case 1 presented with a subcutaneous nodule (dotted area) in the right navel area. The solitary nodule was 15 mm in diameter, slightly firm, and only slightly mobile.

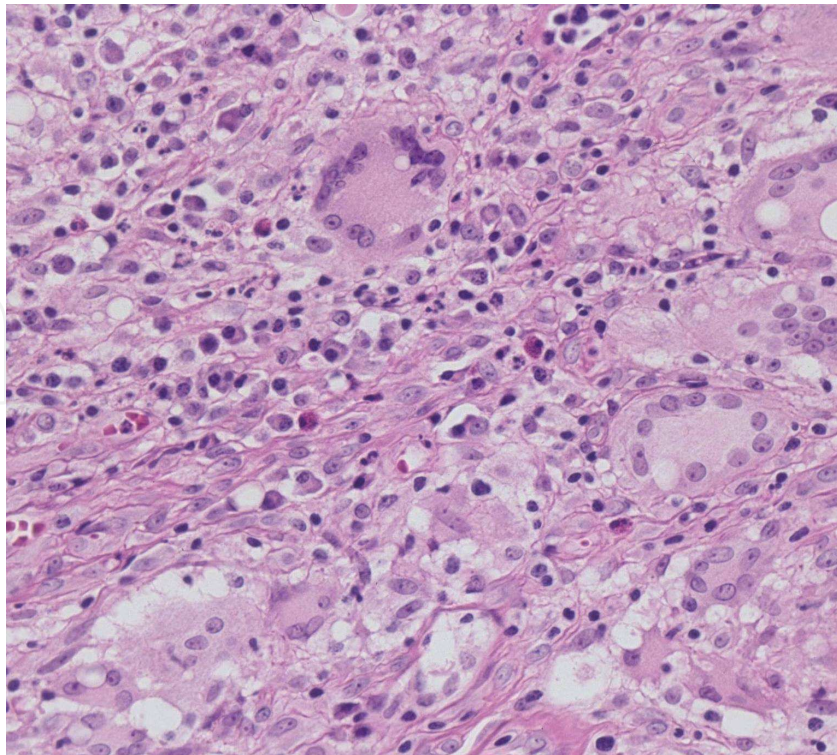


Fig. 2. Case 2 presented with a subcutaneous nodule with an injection scar on the right upper arm. The solitary nodule was 30 × 35 mm in size, slightly firm, and mobile.

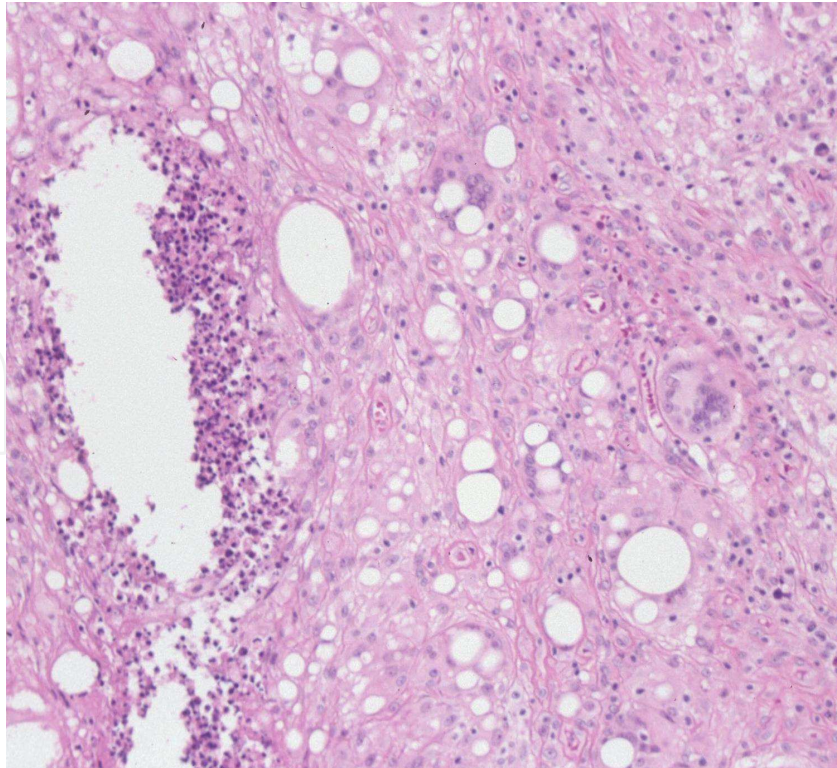


Fig. 3. It showed several eosinophils with multinucleated giant cells in HE staining (original magnification ×400).



Fig. 4. It showed an epithelial granuloma with foreign body multinucleated giant cells containing microspheres and scattered eosinophils. The granuloma with multinucleated giant cells, eosinophils, and numerous vacuoles was located in the subcutaneous tissue (hematoxylin-eosin staining; original magnification $\times 200$).

3. Discussion

Treatments for prostate cancer include hormone therapy, surgical treatment, radiation therapy, and chemotherapy. Although treatment plans differ according to the stage of disease, endocrine therapy is used for clinically localized cancer, locally invasive cancer, and

distant metastasis such as to the bone. Among the endocrine therapies, the first choice for treatment in the initial stage is an LHRH agonist or a combination of an LHRH agonist and an anti-androgen.

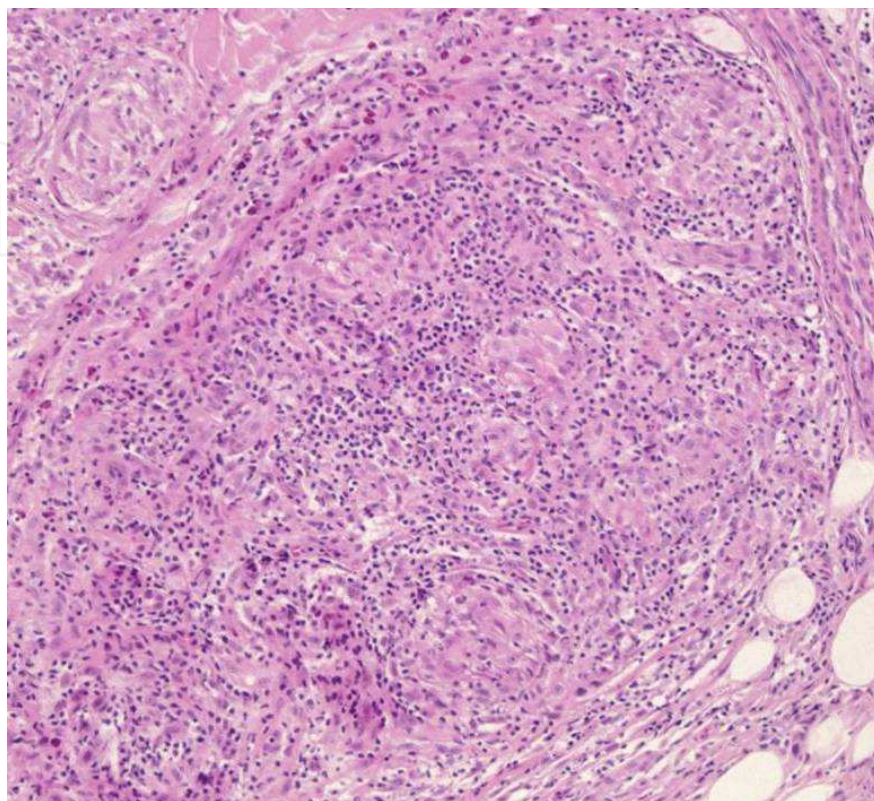


Fig. 5. In the subdermal layer beneath the subcutaneous fat tissue, there was a granuloma, part of which contained multinucleated giant cells (hematoxylin–eosin staining; original magnification $\times 100$).

Leuporelin acetate is a derivative of LHRH with a substituted amino acid sequence; it is a superagonist with an activity approximately 100-fold higher than the natural form. Continuous administration of leuporelin acetate causes downregulation of the LHRH receptor, has an antagonist-like action, and depresses gonadal function. Therefore, it is used for treating sex hormone-dependent diseases. At present, a preparation of leuporelin acetate designed for administration at intervals of 3 months is indicated for prostate cancer and premenopausal breast cancer.

The side effect profile of systemic LHRH agonist injections is below

- fast and irregular heart beat
- bone, muscles, and joint pain
- fainting and fast and irregular breathing and shortness of breath
- numbness and tingling in the hands and feet
- swelling of the eyes and the eyelids
- skin rash or hives and itching
- pains in the chest or tightness of chest and wheezing
- pain in the groin or the legs, especially the calves

If these symptoms are severe, they may require consultation with a physician. Other more common symptoms that are less severe include:

- hot flashes
- burning, itching, redness, and swelling at the injection site
- blurred vision
- dizziness and headaches
- nausea and vomiting and constipation
- gynecomastia (swelling or tenderness and pain of the breasts)
- swelling of feet and lower legs
- trouble sleeping
- decreased size of testicles
- inability to maintain an erection satisfactory for intercourse
- decrease in interest in sex

The side effect profile of local LHRH agonist injections is below²

- erythema
- nodule
- induration
- dermatitis

Previous reports of foreign body granuloma formation resulting from the use of leuprorelin acetate are summarized in Table 1. Sixty-six cases have been reported globally, and most of these reports (58 cases, 87.9%) are from Japan. As mentioned below, the difference in the number of reports between Japan and other countries is believed to be related to the depth

country	Japan: 58 cases Others: 8 cases
disease	prostate cancer: 62 cases central precocious puberty: 4 cases
age	1~89(average: 76.3)
lesion	Upper arm: 30cases Abdomen: 15cases Buttock: 1case Unknown: 20cases
Kind and the number of times of drugs (except for 18 cases of unknown)	1-month depot preparation:12cases 1 ~about60times(average:27.8times)
	3-months depot preparation :36cases 2~7times(average:2.6times)
	<past history of LH-RH agonist:24cases> month depot preparation: 19cases (once~five years; average12.8times) bicalutamide : 3cases(unspecified) goserelin acetate : 2cases(unspecified)

Table 1. Summary of 66 cases

of insertion of the injection needle. All cases were single. The underlying disease was prostate cancer in all cases except four with central precocious puberty. Regarding the cases of prostate cancer, we found that the range of patient ages was 60–89 years, with a mean of 76.3 years, which is consistent with the mean age of prostate cancer onset. The 1-monthly preparation was used in 12 patients, the 3-monthly preparation in 36 patients, and the preparation type was unknown in 18 patients. Among the patients who received the 3-monthly preparation, 24 had a treatment history with LHRH agonists including leuporelin acetate. Most of these patients (19 of them) had previously received the 1-monthly preparation. The injection site was the upper arm in 30 patients, the abdomen in 15 patients, the buttock in 1 patient, and unknown in 20 patients. Among those whose injection sites were known, either the injection sites were changed or the dermatological symptoms were observed at another site in 16 patients. Histologically, all cases had foreign-body granulomatous tissue reaction.

Various opinions on the cause of local reactions to depot leuporelin acetate have been suggested, including the base used and the nature of the preparation itself. Manasco et al. stated that an identical reaction was observed when base alone was injected, and that natural LHRH did not cause a similar reaction. However, Neely et al. administered an alternative drug without the base and observed erythema. In an animal experiment, they also observed a strong reaction when a high concentration of leuporelin acetate was combined with the base. Therefore, the local reaction was thought to be associated not only with the base, but also with the preparation itself.

The leuporelin acetate preparation contained controlled release solid dispersion microspheres comprising lactic acid–glycolic acid copolymers, which slowly disseminated throughout the body. Subsequently, there was a continuous inflammatory response to the leuporelin acetate, and multinucleated giant cells appeared as a result of the recognition of foreign bodies because of the long-term presence of the microspheres themselves. Therefore, histologically, a foreign-body granuloma was formed. The injection dose and needle insertion depth could have also contributed to this finding. There was a 3-fold difference in the leuporelin acetate content between the 1-monthly and 3-monthly preparations. Therefore, the 3-monthly preparation was more likely to cause an inflammatory response. Regarding the needle insertion depth, injections are administered intramuscularly in Europe and the USA, and subcutaneously in Japan. The difference in the number of reported cases between Europe and the USA on one hand and Japan on the other hand may be related to this difference in needle insertion depth.

The number of prostate cancer cases is increasing in Japan with a concomitant increase in the frequency of use of leuporelin acetate. The number of reported cases with granuloma may increase in the future. If a granuloma develops as a result of the use of this preparation, we believe that dermatologists should be obliged to provide appropriate advice to other physicians, such as a change of drug. And physician should pay attention to perform the injection of LA in enough subcutaneous depth and exchange injection sites everytimes.

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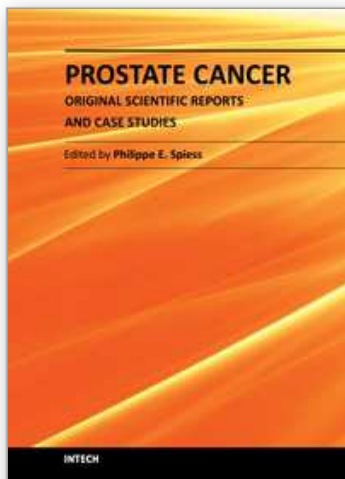
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This book encompasses three sections pertaining to the topics of cancer biology, diagnostic markers, and therapeutic novelties. It represents an essential resource for healthcare professionals and scientist dedicated to the field of prostate cancer research. This book is a celebration of the significant advances made within this field over the past decade, with the hopes that this is the stepping stone for the eradication of this potentially debilitating and/or fatal malignancy.

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